Kam 09/938,112

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=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     15:42:08 ON 20 SEP 2002)
L45           45 S L41 OR L44

=> d que 145
L1          1196 SEA DONOVAN S?/AU
L2        784381 SEA PAIN###
L3         67055 SEA ALLEVIAT?
L4       5735257 SEA REDUC?
L5       5173626 SEA DECREAS?
L6        104498 SEA CLOSTRIDI?
L7         31931 SEA BOTULIN?
L8             1 SEA BERATTI
L9          3871 SEA BUTYRICUM
L10        84589 SEA TETAN?
L11       458558 SEA TOXIN# OR NEUROTOXIN#
L12       275142 SEA NEUROTRANSMI?
L13        15481 SEA SIGNAL(3A) TRANSMI?
L14        94984 SEA SUBSTANCE(A) P
L15       392375 SEA PLASMID#
L16       549607 SEA VECTOR#
L17       232760 SEA CONSTRUCT#
L18      1189738 SEA TARGET?
L23       165111 SEA (FUSION OR CHIMER? OR CHIMAER?)(3N) PROTEIN#
L24            4 SEA L1 AND L2
L25       106941 SEA ((L3 OR L4 OR L5) OR TREAT? OR THERAP?) (5A) L2
L26          616 SEA L25 AND ((L6 OR L7 OR L8 OR L9 OR L10))
L27          464 SEA L26 AND L11
L28            4 SEA L27 AND L23
L29           21 SEA L27 AND L14
L30           22 SEA L27 AND L12
L32            2 SEA L27 AND ((L15 OR L16 OR L17))
L33           77 SEA ((L6 OR L7 OR L8 OR L9 OR L10))(5A) L11(5A)(CONJUGAT? OR
                 FUSION# OR CHIMER? OR CHIMAER?) AND (L12 OR L13)
L34            7 SEA L2 AND L33
L35            3 SEA ((L6 OR L7 OR L8 OR L9 OR L10))(5A) L11(5A)(CONJUGAT? OR
                 FUSION# OR CHIMER? OR CHIMAER?) (5A) L2
L36           12 SEA ((L6 OR L7 OR L8 OR L9 OR L10))(5A) L11(5A)(CONJUGAT? OR
                 FUSION# OR CHIMER? OR CHIMAER?) AND L2
L37           63 SEA ((L6 OR L7 OR L8 OR L9 OR L10)) AND L14 AND EXPRESS?
L38            9 SEA L37 AND L2
L40           46 SEA L24 OR L28 OR L29 OR L30 OR L32 OR L34 OR L35 OR L36 OR
                 L38
L41           31 DUP REM L40 (15 DUPLICATES REMOVED)
L42         1406 SEA L18 (5A)(L12 OR L13)
L43           28 SEA L42 AND ((L6 OR L7 OR L8 OR L9 OR L10))
L44           14 DUP REM L43 (14 DUPLICATES REMOVED)
L45           45 SEA L41 OR L44


=> d ibib abs 145 1-45

L45  ANSWER 1 OF 45     MEDLINE
ACCESSION NUMBER:    2002470902     IN-PROCESS
DOCUMENT NUMBER:     22218001   PubMed ID: 12105193
TITLE:               Inhibition of Release of Neurotransmitters from
                     Rat Dorsal Root Ganglia by a Novel Conjugate of a
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Kam 09/938,112

Clostridium botulinum Toxin A Endopeptidase Fragment and Erythrina cristagalli Lectin.

AUTHOR: Duggan Michael J; Quinn Conrad P; Chaddock John A; Purkiss John R; Alexander Frances C G; Doward Sarah; Fooks Sarah J; Friis Lorna M; Hall Yper H J; Kirby Elizabeth R; Leeds Nicola; Moulsdale Hilary J; Dickenson Anthony; Green G Mark; Rahman Wahida; Suzuki Rie; Shone Clifford C; Foster Keith A

CORPORATE SOURCE: Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom and the University College London, University College, Gower Street, London WC1E 6BT, United Kingdom.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Sep 20) 277 (38) 34846-52.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20020917
Last Updated on STN: 20020917

AB **Clostridial neurotoxins** potently and specifically inhibit **neurotransmitter** release in defined cell types. Here we report that a catalytically active derivative (termed LH(N)/A) of the type A **neurotoxin** from **Clostridium botulinum** has been coupled to a lectin obtained from Erythrina cristagalli to form a novel conjugate. This conjugate exhibits an in vitro selectivity for nociceptive afferents compared with the anatomically adjacent spinal neurons, as assessed using in vitro primary neuronal culture systems to measure inhibition of release of **neurotransmitters**. Chemical conjugates prepared between E. cristagalli lectin and either natively sourced LH(N)/A or recombinant LH(N)/A purified from Escherichia coli are assessed, and equivalence of the recombinant material are demonstrated. Furthermore, the dependence of inhibition of **neurotransmitter** release on the cleavage of SNAP-25 is demonstrated through the use of an endopeptidase-deficient LH(N)/A conjugate variant. The duration of action of inhibition of **neurotransmitter** released by the conjugate in vitro is assessed and is comparable with that observed with **Clostridium botulinum neurotoxin**. Finally, in vivo electrophysiology shows that these in vitro actions have biological relevance in that sensory transmission from nociceptive afferents through the spinal cord is significantly attenuated. These data demonstrate that the potent endopeptidase activity of **clostridial neurotoxins** can be selectively retargeted to cells of interest and that inhibition of release of **neurotransmitters** from a neuronal population of **therapeutic** relevance to the **treatment** of **pain** can be achieved.

L45 ANSWER 2 OF 45 MEDLINE

ACCESSION NUMBER: 2001680312 MEDLINE

DOCUMENT NUMBER: 21583314 PubMed ID: 11727162

TITLE: [Early **pain reduction** in the **treatment** of spasticity after a single injection of **botulinum** A **toxin**].
Fruhe Schmerzreduktion in der Therapie von Spastik nach einmaliger **Botulinustoxin**-A-Injektion.

AUTHOR: Chalkiadaki A; Rohr U P; Hefter H

CORPORATE SOURCE: Neurologische Klinik, Heinrich-Heine-Universitat, Dusseldorf.. chalkiadaki@med.uni-duesseldorf.de

Search completed by David Schreiber 308-4292

Kam 09/938,112

SOURCE: DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, (2001 Nov 30) 126 (48) 1361-4.
Journal code: 0006723. ISSN: 0012-0472.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020125
Entered Medline: 20020107

AB HISTORY, ADMISSION FINDINGS AND DIAGNOSIS: After stem-cell transplantation a 45-year-old woman (case 1) had an attack of general hypoxia requiring resuscitation. She then developed a quadriplegia and spasticity of all limbs notably of the right arm and a severe **pain** syndrome which had to be **treated** by oral and intravenous analgesics. Immobilisation and secondary complications aggravated the already difficult situation. In the 2nd case a 66-year-old woman was admitted to our outpatient clinic with long-standing left-sided spastic hemiparesis after territorial infarction of the right middle cerebral artery. Beside the spasticity she also suffered from a distinct pain syndrome which did not respond to any oral analgesics. TREATMENT AND COURSE: For the treatment of the main symptoms, both patients received intramuscular injections of 1000 MU **botulinum toxin** A (Dysport(R) Ipsen Pharma). Astonishingly, both patients experienced pain relief the next day, whereas spasticity started to respond only 5-6 days later. CONCLUSIONS: In our experience pain relief after **botulinum toxin** A injections occurs not only due to reduced muscle hyperactivity, especially when such a temporal dissociation between pain relief and muscle relaxation appears as in the two cases reported above. Rather, we believe that **botulinum toxin** A interferes with the release of other **neurotransmitters** e. g. **substance P** (SP) and calcitonine-gene-related-peptide (CGRP) having a key function in the nociceptive cascade.

L45 ANSWER 3 OF 45 MEDLINE
ACCESSION NUMBER: 2001325277 MEDLINE
DOCUMENT NUMBER: 21218322 PubMed ID: 11320866
TITLE: [**Reduction** of **pain** and muscle spasms by **botulinum toxin** A].
Reduktion von Schmerzen und Muskelanspannung durch **Botulinum-Toxin** A.
AUTHOR: Kelm S; Gerats G; Chalkiadaki A; Hefter H
CORPORATE SOURCE: Neurologische Klinik der Heinrich-Heine-Universitat Dusseldorf, Moorenstr. 5, 40225 Dusseldorf..
Stefan.Kelm@uni-duesseldorf.de
SOURCE: NERVENARZT, (2001 Apr) 72 (4) 302-6.
Journal code: 0400773. ISSN: 0028-2804.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB **Botulinum toxin** A (BoNT-A) develops its muscle-relaxing effect by the inhibition of acetylcholine (ACh) release. This **toxin** is also known to relieve muscular pain in different

Search completed by David Schreiber 308-4292

disorders. Conspicuously, pain in some patients responds earlier and sometimes even better than muscle tension, indicating that the effect of BoNT-A on pain is not only due to inhibition of ACh release. A questionnaire was distributed to 88 patients suffering from cervical dystonia (CD). Thirty-five completed questionnaires could be used for data analysis. After intramuscular injections of BoNT-A, patients with CD experience significant **reductions** in **pain** which sometimes occur significantly earlier than the improvements in head posture. In the iris sphincter muscle of the rabbit and in dorsal root ganglion cells (DRG) of the rat, inhibition of the release of **substance P** by BoNT-A has been shown experimentally, and BoNT-C has been proven to develop endopeptidase activity toward **substance P** (SP) in vitro. Findings in the current literature and our observations allow the conclusion that **alleviation** of muscle **pain** by BoNT-A may also be due to an effect on the release of nociceptive neuropeptides, among which SP seems to have a key function.

L45 ANSWER 4 OF 45 MEDLINE
ACCESSION NUMBER: 2001325272 MEDLINE
DOCUMENT NUMBER: 21218317 PubMed ID: 11320861
TITLE: [**Botulinum toxin** A for the **treatment** of headache disorders and pericranial **pain** syndromes].
Botulinum-Toxin A in der Therapie von Kopfschmerzerkrankungen und perikranialen Schmerzsyndromen.
AUTHOR: Gobel H; Heinze A; Heinze-Kuhn K; Austermann K
CORPORATE SOURCE: Neurologisch-verhaltensmedizinische Schmerzklinik Kiel in Kooperation mit der Universitat Kiel, Heikendorfer Weg 9-27, 24149 Kiel.. kiel@Schmerzklinik.de
SOURCE: NERVENARZT, (2001 Apr) 72 (4) 261-74. Ref: 104
Journal code: 0400773. ISSN: 0028-2804.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

AB For 20 years **botulinum toxin** A has been used for the treatment of a variety of disorders characterised by pathologically increased muscle contraction. Recently, treatment of tension headache, migraine, cluster headache, and myofascial **pain** syndromes of neck, shoulder girdle, and back with **botulinum toxin** A has become a rapidly expanding new field of research. Several modes of action are discussed for these indications. The blockade of cholinergic innervation reduces muscular hyperactivity for 3 to 6 months. Degenerative changes in the musculoskeletal system of the head and neck are prevented. Nociceptive afferences and blood vessels of the pericranial muscles are decompressed and muscular trigger points and tender points are resolved. The normalisation of muscle spindle activity leads to a normalisation of muscle tone and central control mechanisms of muscle activity. Oromandibular dysfunction is eliminated and muscular stress removed. However, the effect of **botulinum toxin** A cannot be explained by muscular actions only. Its retrograde uptake into the central nervous system modulates the **expression** of **substance**

P and enkephalins in the spinal cord and nucleus raphe. Recent findings suggest an inhibition of sterile inflammation which may lead to a blockade of the neurogenic inflammation believed to be the pathophysiological substrate of primary headache disorders. The efficacy of **botulinum toxin** A in the **treatment** of **pain** disorders is being investigated in several studies at the moment. The results and experiences obtained so far present new alternatives in the **treatment** of chronic **pain** disorders. The practical use of **botulinum toxin** A is demonstrated.

L45 ANSWER 5 OF 45 MEDLINE
ACCESSION NUMBER: 2001266781 MEDLINE
DOCUMENT NUMBER: 21256883 PubMed ID: 11357237
TITLE: Pharmacology and immunology of **botulinum toxin** serotypes.
AUTHOR: Aoki K R
CORPORATE SOURCE: Allergan, Inc., Irvine, CA 92623, USA.
SOURCE: JOURNAL OF NEUROLOGY, (2001 Apr) 248 Suppl 1 3-10. Ref: 81
Journal code: 0423161. ISSN: 0340-5354.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB **Botulinum toxin** preparations can provide patients with a therapeutic modality that may improve both their medical condition and quality of life. The mechanism of action of the various **botulinum toxin** preparations and serotypes is similar: they all block **neurotransmitter** release. The majority of clinical conditions treated are based upon the targeted temporary chemodenervation of the selected organ. The antinociceptive effects of **botulinum toxin** type A (BTX-A), based on preclinical studies and clinical experiences in **treating** movement disorders and other **painful** conditions, will also be reviewed to illustrate how this compound may act as it alleviates the discomfort associated with various conditions. Chronic therapies with preparations with the lowest amount of **neurotoxin** protein provide the best chance for long-term therapy by minimizing the potential of the patient to form neutralizing antibodies. Differences in formulations or serotypes impart unique efficacy and safety profiles and thus does not support a simple dose ratio conversion between products.

L45 ANSWER 6 OF 45 MEDLINE
ACCESSION NUMBER: 2000225550 MEDLINE
DOCUMENT NUMBER: 20225550 PubMed ID: 10762359
TITLE: Evidence for nonvesicular nitric oxide release evoked by nerve activation.
AUTHOR: Olgart C; Gustafsson L E; Wiklund N P
CORPORATE SOURCE: Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden.. caroline.olgart@fyfa.ki.se
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2000 Apr) 12 (4) 1303-9.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France

Search completed by David Schreiber 308-4292

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000621

AB The gaseous nature of nitric oxide (NO) has led to the general assumption that its release from neurons during nerve stimulation is independent of vesicular storage. However, recent findings have shown that NO can exist intracellularly as part of more stable bioactive molecules, suggesting that the role of vesicular exocytosis for NO release cannot be excluded simply based on the chemical nature of NO itself. We have used **botulinum** toxin B (BTX B) to directly address the role of vesicular exocytosis for NO release. BTX B cleaves the synaptic vesicle protein synaptobrevin/VAMP, and by this inhibits Ca++-mediated exocytic release of **neurotransmitters**. As a **target** organ we used the guinea-pig enteric nervous system, which innervates the gastrointestinal tract, and in which both classical neurotransmitters as well as NO are released and influence smooth muscle activity. As expected, BTX B (0.1 microM) blocked the nerve stimulation-induced cholinergic and tachykininergic smooth muscle contractions, and markedly inhibited the nerve stimulation-evoked release of [3H]-choline. In contrast, BTX B (0.1 microM) had no effect on nerve stimulation-evoked relaxations, which were equally inhibited by an NO-synthase inhibitor as well as by a selective inhibitor of soluble guanylyl cyclase. In addition, nerve stimulation-evoked NO synthase-dependent outflow of NO/NO2- was unaffected by BTX B (0.1 microM). These findings suggest that the neuronal release of endogenous NO is independent of intact synaptobrevin/VAMP, and therefore provide further evidence that nerve-mediated release of further NO is nonvesicular.

L45 ANSWER 7 OF 45 MEDLINE
ACCESSION NUMBER: 1999413312 MEDLINE
DOCUMENT NUMBER: 99413312 PubMed ID: 10485302
TITLE: Safety and immunogenicity of Haemophilus influenzae type b-tetanus toxoid conjugate, presented in a dual-chamber syringe with diphtheria-tetanus-pertussis and inactivated poliomyelitis combination vaccine.
AUTHOR: Langue J; Ethevenaux C; Champsaur A; Fritzell B; Begue P; Saliou P
CORPORATE SOURCE: GLyRPA, St Fons, France.
SOURCE: EUROPEAN JOURNAL OF PEDIATRICS, (1999 Sep) 158 (9) 717-22.
Journal code: 7603873. ISSN: 0340-6199.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991021

AB The safety and immunogenicity of combining two established vaccines, polyribosyl ribitol phosphate conjugated to tetanus toxoid (PRP-T) (ActHIB, Pasteur Merieux Connaught, Lyon, France) and diphtheria-tetanus-whole cell pertussis and inactivated poliovirus vaccine (DTP-IPV)

Search completed by David Schreiber 308-4292

(Tetracoq, Pasteur Merieux Connaught, Lyon, France) were evaluated using a new dual-chamber syringe delivery system. Results were compared with those obtained when the two combination vaccines were either administered separately (two sites) or reconstituted manually and injected at a single site. A total of 487 2-month-old infants were enrolled in this study by 61 paediatricians in France. Infants were randomised to receive three immunisations of PRP-T and DTP-IPV at 2, 3 and 4 months of age, given either with the dual-chamber syringe (n = 213), as separate injections (n = 215), or as a single manually reconstituted injection (n = 59). Blood samples were taken prior to the first immunisation and 4 weeks after the third immunisation for the measurement of antibody titres. Infants were monitored by the parents for 3 days after each immunisation to detect local and systemic reactions. Local and systemic reactions occurring the 3 days following immmunisation were as expected for the combination vaccines used. Safety of the vaccination using the dual-chamber syringe was as good as, if not slightly better than, that for the two vaccines administered separately. After the first immunisation, **pain** and unusual crying were significantly more frequent in infants who received two injections, compared to those who were immunised with the dual-chamber syringe. Serological responses were good for all antigens in the three groups and there was no evidence for any immunological interference. Almost all subjects in each group achieved levels of antibodies considered to be protective for all antigens. There were no clinically relevant differences in antibody response between any of the groups. The dual-chamber and separate injection methods of vaccination were equivalent according to a pre-defined criterion (percentage of infants with anti-PRP antibody titres > or =1.0 microg/ml). Results from this study suggest that the two vaccines, PRP-T and DTP-IPV, may be safely and effectively administered in infants using the new dual-chamber syringe. This presentation provides an innovative strategy to combine different vaccines that are not yet available as a single formulation.

L45 ANSWER 8 OF 45 MEDLINE
ACCESSION NUMBER: 1998420616 MEDLINE
DOCUMENT NUMBER: 98420616 PubMed ID: 9748792
TITLE: [Membrane metalloendopeptidase (CD10/CALLA): distribution, physiologic and pathophysiologic functions and its inhibitors].
Membranska metaloendopeptidaza (CD10/CALLA): rasprostranjenost, fizioloske i patofizioloske funkcije i inhibitori.
AUTHOR: Stanovic S; Boranic M
CORPORATE SOURCE: Institut Ruder Boskovic Zavod za molekularnu medicinu, Laboratorij za eksperimentalnu hematologiju, imunologiju i onkologiju, Zagreb.
SOURCE: LIJECNICKI VJESNIK, (1998 May) 120 (5) 131-7. Ref: 56
Journal code: 0074253. ISSN: 0024-3477.
PUB. COUNTRY: Croatia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Serbo-Croatian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981113
AB Membrane metalloendopeptidase EC 3.4.24.11 (Enkephalinase, neutral endopeptidase, NEP) is a cellular ectoenzyme, immunophenotypically

Search completed by David Schreiber 308-4292

identified as the leukocyte cluster of differentiation CD10 or CALLA (common acute lymphoblastic leukemia antigen). Immunological, biochemical and molecular biology techniques have identified tis cell membrane feature in various organs: brain, cardiovascular system, lung, placenta, kidney etc. The CD10 immunophenotype is a common feature of lymphoblasts in acute lymphoid leukemia not **expressing** the T- or B-markers. The enzymatic activity of CD10/NEP possibly influences normal lymphocyte ontogeny by proteolytic cleavage of the regulatory peptides. The substrates of CD10/NEP in the kidneys are (see the list of abbreviations) ANP, adrenomedullin and PAMP; in the brain, the substrates are enkephalins and oxytocin; in the lung, bombesin, BLP, GRP, neuromedin C, **substance P** and neurokinin A; in the cardiovascular system, angiotenisin II, bradykinin and CGRP; in the gut, VIP; on the neutrophil membrane, fMLP etc. Some substrates are not strictly tissue-specific, e.g. **substance P**. Preclinical and clinical trials explore possibilities of therapeutic application of the inhibitors of neutral endopeptidase, such as thiorphan in the management of **pain**, diarrhoea, depression, arterial hypertension and asthma. Other possibilities of application include the treatment of hyalinomembranous disease and prevention of neurotoxicosis in **tetanus** and botulism.

L45 ANSWER 9 OF 45 MEDLINE
ACCESSION NUMBER: 97441748 MEDLINE
DOCUMENT NUMBER: 97441748 PubMed ID: 9295967
TITLE: [Action mechanisms of **botulinum** neurotoxins and **tetanus** neurotoxins].
Mecanismes d'action des neurotoxines botuliques et de la neurotoxine **tetanique**.
AUTHOR: Deloye F; Doussau F; Poulain B
CORPORATE SOURCE: Laboratoire de Neurobiologie Cellulaire et Moleculaire, UPR 9040 du CNRS, Gif-sur-Yvette.
SOURCE: COMPTES RENDUS DES SEANCES DE LA SOCIETE DE BIOLOGIE ET DE SES FILIALES, (1997) 191 (3) 433-50. Ref: 85
Journal code: 7505439. ISSN: 0037-9026.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971002

AB **Tetanus** (TeNT) neurotoxin and **botulinum** (BoNT, serotypes A-G) neurotoxins are di-chain bacterial proteins of MW-150 kDa which are also termed as **clostridial** neurotoxins. They are the only causative agents of two severe neuroparalytic diseases, namely **tetanus** and botulism. The peripheral muscle spasms which characterise **tetanus** are due to a blockade of inhibitory (GABAergic and glycinergic) synapses in the central nervous system leading to a motor neurones desinhibition. In contrast, botulism symptoms are only peripheral. They are consequent to a near irreversible and highly selective inhibition of acetyl-choline release at the motor nerve endings innervating skeletal muscles. During the past decade, the cellular and molecular modes of action of **clostridial** neurotoxins has been near completely elucidated. After a binding step of the neurotoxins to specific membrane acceptors located only on nerve terminals, BoNTs and

TeNT are internalized into neurons. Inside their target neurones, the intracellularly active moiety (their light chain) is translocated from the endosomal compartment to the cytosol. The neurotoxins' light chains are zinc-dependent (endopeptidases which are specific for one among three synaptic proteins (VAMP/synaptobrevin, syntaxin or SNAP-25) implicated in **neurotransmitter** exocytosis. The presence of distinct **targets** for BoNTs and TeNT correlates well with the observed quantal alterations of neurotransmitter release which characterize certain toxin serotypes. In addition, evidence for a second, non-proteolytic, inhibitory mechanism of action has been provided recently. Most likely, this additional blocking action involves the activation of neurone transglutaminases. Due to their specific action on key proteins of the exocytosis apparatus, **clostridial** neurotoxins are now widely used as molecular tools to study exocytosis.

L45 ANSWER 10 OF 45 MEDLINE
ACCESSION NUMBER: 96301864 MEDLINE
DOCUMENT NUMBER: 96301864 PubMed ID: 8723218
TITLE: Functional reconstitution of KCl-evoked, Ca(2+)-dependent acetylcholine release system in Xenopus oocytes microinjected with presynaptic plasma membranes and synaptic vesicles.
AUTHOR: Canals J M; Ruiz-Avila L; Canti C; Solsona C; Marsal J
CORPORATE SOURCE: Departament de Biologia Cellular i Anatomia Patologica, Facultat de Medicina, Hospital de Bellvitge, Universitat de Barcelona, Spain.
SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1996 Apr 15) 44 (2) 106-14.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19970203
Entered Medline: 19960926

AB We have developed a new method for the generation of functionally active presynaptic chimeras in Xenopus laevis oocytes. Frog oocytes injected with presynaptic subcellular fractions extracted from the electric organ of Torpedo marmorata release acetylcholine in a calcium-dependent manner upon chemical stimulation. Neither oocytes injected without presynaptic plasma membranes nor oocytes injected with ghost erythrocyte plasma membrane instead of presynaptic plasma membrane release acetylcholine. This suggests that specific presynaptic components necessary for KCl-evoked, Ca(2+)-dependent acetylcholine release become functionally integrated in the Xenopus laevis oocytes. Moreover, rhodaminated presynaptic plasma membranes and the synaptic vesicle protein synaptophysin are detected on the oocyte surface by fluorescence or immunofluorescence, respectively, showing that the injected presynaptic components are incorporated into the membrane of the frog oocyte. Furthermore, **Botulinum** neurotoxin type A, a specific blocker of acetylcholine release in the neuromuscular junction, inhibits the neurotransmitter release from the chimerical oocytes. This suggests that targets for toxin action are also functionally incorporated in the oocyte upon injection of membranous presynaptic components. Our results show that oocytes injected with presynaptic components behave as cholinergic nerve ending chimeras, at least in terms of **neurotransmitter** release and toxin **targets**. The system bypasses some problems associated with messenger RNA expression

because not only proteins, but native presynaptic components are incorporated. This new technique may provide a useful approach for electrophysiological and pharmacological studies in order to characterize the synaptic transmission.

L45 ANSWER 11 OF 45 MEDLINE
ACCESSION NUMBER: 96052149 MEDLINE
DOCUMENT NUMBER: 96052149 PubMed ID: 8542756
TITLE: Quantal **neurotransmitter** release and the **clostridial** neurotoxins' **targets**.
AUTHOR: Poulain B; Molgo J; Thesleff S
CORPORATE SOURCE: Laboratoire de Neurobiologie Cellulaire et Moleculaire, Centre National de la Recherche Scientifique, Gif sur Yvette, France.
SOURCE: CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY, (1995) 195 243-55. Ref: 77
Journal code: 0110513. ISSN: 0070-217X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960227
Last Updated on STN: 19970203
Entered Medline: 19960213

L45 ANSWER 12 OF 45 MEDLINE
ACCESSION NUMBER: 94377259 MEDLINE
DOCUMENT NUMBER: 94377259 PubMed ID: 7916455
TITLE: [Molecular mechanism of action of **tetanus** toxin and **botulinum** neurotoxins].
Mecanisme d'action moleculaire de la toxine **tetanique** et des neurotoxines botuliques.
AUTHOR: Poulain B
CORPORATE SOURCE: Laboratoire de Neurobiologie Cellulaire et Moleculaire, CNRS, Gif-sur-yvette, France.
SOURCE: PATHOLOGIE BIOLOGIE, (1994 Feb) 42 (2) 173-82. Ref: 121
Journal code: 0265365. ISSN: 0369-8114.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19970203
Entered Medline: 19941020

AB **Tetanus** toxin and **botulinum** neurotoxins are di-chain proteins of 150 kD molecular weight. They are produced by bacteria of the **Clostridium** genus. These toxins act on the nervous system by inhibiting neurotransmitter release (glycine and GABA in the case of **tetanus** toxin; acetylcholine in the case of **botulinum** neurotoxins) thus inducing the spastic or flaccid paralysis that characterizes **tetanus** and botulism, respectively. Their cellular mechanism of action involves three main steps, namely binding to the neurone membrane, internalization and intracellular blockade of the

release mechanism for neurotransmitters. Membrane acceptors for these toxins are not yet fully identified; they would consist of membrane gangliosides and proteins. The internalization step would be achieved by endocytosis. Recent findings show that both binding and internalization are mediated only by the heavy chain of the toxins whereas the intracellular blockade of neurotransmitter release involves their light chain alone. The light chain has been identified as a zinc metalloprotease and its substrates would be proteins involved in the **neurotransmitter** release mechanism. The **target** of **tetanus** toxin and of **botulinum** neurotoxin type B is VAMP/synaptobrevin, a membrane protein of the synaptic vesicles of nerve cell terminals.

L45 ANSWER 13 OF 45 MEDLINE
ACCESSION NUMBER: 94330801 MEDLINE
DOCUMENT NUMBER: 94330801 PubMed ID: 8053763
TITLE: [Immunogenicity and tolerability of Haemophilus b-tetanus protein conjugate (PRP-T) in children with sickle cell anemia].
Immunogenicite et tolerance du vaccin anti-Haemophilus b conjugue a la proteine tetanique (PRP-T) chez l'enfant drepanocytaire.
AUTHOR: de Montalembert M; Begue P; Fritzell B; Houmeau P
CORPORATE SOURCE: Service du Centre de la Drepanocytose et de la Thalassemie de l'Hopital Necker-Enfants Malades, Paris.
SOURCE: ARCHIVES FRANCAISES DE PEDIATRIE, (1993 Dec) 50 (10) 863-6.
Journal code: 0372421. ISSN: 0003-9764.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940914
Last Updated on STN: 19940914
Entered Medline: 19940906

AB BACKGROUND. Infants and young children with sickle cell anemia are at increased risk of infection with Haemophilus influenzae type b. This report describes the immunogenicity and safety of Haemophilus b conjugate vaccine in such children. POPULATION AND METHODS. One hundred and eleven children aged 6 months-11 years (mean: 3.7 years) were studied. They belonged to a cohort of over 600 children in the Paris area that have sickle cell anemia. After parental consent, they were given one injection (intramuscularly or subcutaneously) of Haemophilus influenzae type b-tetanus toxoid conjugate vaccine (0.5 ml). Any adverse reactions during the following 3 days were noted. Titers of specific antibodies were measured just before injection, one month, and one year later. RESULTS. The vaccine was well tolerated, with only local reactions: erythematous reactions in 5 children and **pain** in 30. In the children aged 6 months-3 years, the mean antibody titers increased from 0.09 to 20.6 micrograms/ml, 1 month after the vaccination; in those aged 3-11 years, the mean titer increased from 0.44 to 56.86 micrograms/ml. One year after vaccination, the titers measured in 61 children were over 1 microgram/ml in 92% of children aged 6 months-3 years and in 100% of the older children. CONCLUSION. This type of vaccine is immunogenic and well tolerated. Thus the vaccination schedule recommended for children with sickle cell anemia aged over 6 months is the same as that for normal children.

L45 ANSWER 14 OF 45 MEDLINE

Search completed by David Schreiber 308-4292

Kam 09/938,112

ACCESSION NUMBER: 89238278 MEDLINE
DOCUMENT NUMBER: 89238278 PubMed ID: 2854607
TITLE: Effects of neurotoxicants on synaptic transmission: lessons learned from electrophysiological studies.
AUTHOR: Atchison W D
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Michigan State University, East Lansing 48824.
CONTRACT NUMBER: ES00178 (NIEHS)
ES03299 (NIEHS)
NS20683 (NINDS)
SOURCE: NEUROTOXICOLOGY AND TERATOLOGY, (1988 Sep-Oct) 10 (5) 393-416. Ref: 206
Journal code: 8709538. ISSN: 0892-0362.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890616

AB A number of environmentally-important neurotoxicants affect chemical synaptic transmission in the peripheral and central nervous system. These include heavy metals such as lead, mercury, cadmium and tin; organophosphates; pyrethroid insecticides, and 2,5-hexanedione. Electrophysiological techniques including intracellular microelectrode recording of nerve-evoked and spontaneously occurring synaptic potentials, iontophoresis of neurotransmitter, and voltage clamp of presynaptic and postsynaptic membrane ionic current have proven to be especially useful in analyzing the cellular mechanisms by which these toxicants affect neurotransmission. The process of synaptic transmission can be broadly subdivided into those processes associated with transmitter synthesis, storage and release and sometimes termination of transmitter action (presynaptic processes), and those processes associated with binding of transmitter to its receptors on the receiving cell, activation of the receptor-associated ionic channel and degradation of chemical transmitter (postsynaptic processes). The processes associated with release of **neurotransmitter** are the **target** of a number of naturally-occurring toxins and environmentally important toxicants. General mechanisms by which these agents disrupt presynaptic processes associated with transmission include: prevention or disruption of axonal excitability (pyrethroid insecticides); disruption of calcium-dependent neurotransmitter release (heavy metals, antibiotics, certain snake and spider venom toxins, **botulinum** toxin); and disruption of intracellular buffering of calcium (heavy metals), Mechanisms by which these agents may disrupt postsynaptic processes include effects on transmitter degradation (organophosphates) or effects on the postsynaptic membrane receptors or associated ionic channels (organophosphates, antibiotics, and perhaps pyrethroids). Microelectrode studies have shown that cadmium, lead and mercury (organic and inorganic forms) suppress release of neurotransmitter by presynaptic mechanisms and increase spontaneous discharge of transmitter quanta from the presynaptic nerve terminal. This has led to the suggestion that a component of synaptic toxicity of these agents entails block of Ca entry into and buffering by the presynaptic nerve terminals. Conventional and patch voltage clamp studies have been used to measure effects of neurotoxicants on ionic currents carried through voltage-sensitive and receptor-operated ionic

Search completed by David Schreiber 308-4292

channels.(ABSTRACT TRUNCATED AT 400 WORDS)

L45 ANSWER 15 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:595499 HCAPLUS
DOCUMENT NUMBER: 137:145554
TITLE: Methods of administering botulinum toxin
INVENTOR(S): Walker, Patricia S.
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U. S. Ser. No. 730,237.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002107199	A1	20020808	US 2002-51952	20020117
US 2002086036	A1	20020704	US 2000-730237	20001205

PRIORITY APPLN. INFO.: US 2000-730237 A2 20001205
AB Methods for treating conditions in an animal or human subject are disclosed. The conditions may be **pain**, skeletal muscle conditions, smooth muscle conditions, glandular conditions and cosmetic conditions. The methods comprise the step of administering a Clostridium neurotoxin component or Clostridium neurotoxin component-encoding DNA to the subject using a needleless syringe.

L45 ANSWER 16 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:521523 HCAPLUS
DOCUMENT NUMBER: 137:73273
TITLE: Adrenergic receptor ligand-**neurotoxin** conjugates and methods for **treating pain**
INVENTOR(S): Gil, Daniel W.; Aoki, Kei Roger
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053177	A2	20020711	WO 2001-US48651	20011214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-751053 A 20001229
OTHER SOURCE(S): MARPAT 137:73273
AB Agents for **treating pain**, methods for producing the agents, and methods for **treating pain** by

administration to a patient of a therapeutically effective amt. of the agent, are disclosed. The agent may include a **clostridial neurotoxin**, a fragment or a deriv. thereof, attached to a targeting component, wherein the targeting component is selected form a group consisting of compds. which selectively binds at the .alpha.2b or .alpha.2b/.alpha.2c adrenergic receptor subtype(s) as compared to other binding sites, e.g. the .alpha.2a adrenergic receptor subtype.

L45 ANSWER 17 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:505315 HCAPLUS
DOCUMENT NUMBER: 137:75525
TITLE: Biodetectors targeted to specific ligands
INVENTOR(S): Contag, Pamela R.; Contag, Christopher H.; Benaron, David A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 844,336.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002086424	A1	20020704	US 1998-183566	19981030
CA 2251826	AA	19971030	CA 1997-2251826	19970421
CN 1219239	A	19990609	CN 1997-193894	19970421

PRIORITY APPLN. INFO.: US 1996-15633P P 19960419
US 1997-844336 A2 19970418

AB The present invention relates to biodetectors for detecting and quantifying mols. in liq., gas, or matrixes. More specifically, the present invention relates to biodetectors comprising a mol. switching mechanism to express a reporter gene upon interaction with target substances. The invention further relates to methods using such biodetectors for detecting and quantifying selected substances with high specificity and high sensitivity. The biodetector comprises (a) a signal converting element comprising an extracellular ligand-specific moiety, e.g., an antibody or fragment, and an intracellular signal transforming domain activated by binding of ligand to the extracellular ligand-specific moiety; (b) a transducer activated by the activated intracellular signal transforming domain; (c) a responsive element activated by active transducer; and (d) a reporter gene operably linked to the responsive element. The activation of the responsive element causes expression of the reporter gene.

L45 ANSWER 18 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:403839 HCAPLUS
DOCUMENT NUMBER: 136:395977
TITLE: **Clostridial toxin** derivatives able to modify peripheral sensory afferent functions
INVENTOR(S): Foster, Keith Alan; Duggan, Michael John; Shone, Clifford Charles
PATENT ASSIGNEE(S): The Speywood Laboratory, Ltd., UK; Microbiological Research Authority
SOURCE: U.S., 18 pp., Cont.-in-part of U.S. Ser. No. 945,037.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English

Search completed by David Schreiber 308-4292

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6395513	B1	20020528	US 1999-447356	19991122
WO 9633273	A1	19961024	WO 1996-GB916	19960416
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5989545	A	19991123	US 1998-945037	19980112

PRIORITY APPLN. INFO.: GB 1995-8204 A 19950421
WO 1996-GB916 A2 19960416
US 1998-945037 A2 19980112

AB The invention discloses an agent specific for peripheral sensory afferents. The agent may inhibit the transmission of signals between a primary sensory afferent and a projection neuron by controlling the release of at least one **neurotransmitter** or neuromodulator from the primary sensory afferent. The agent may be used in or as a pharmaceutical for the **treatment** of **pain**, particularly chronic **pain**. Agents of the invention include a modified **clostridial neurotoxin** fused to a targeting moiety. Prepn. and biol. testing of a conjugate of NGF with the LHN fragment of **botulinum neurotoxin** A are included.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 19 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:241331 HCAPLUS
DOCUMENT NUMBER: 136:273210
TITLE: **Clostridial toxin** derivatives and methods for **treating pain**
INVENTOR(S): **Donovan, Stephen**
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Ser. No. 625,098.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002037833	A1	20020328	US 2001-922093	20010803

PRIORITY APPLN. INFO.: US 2000-489667 A2 20000119
US 2000-625098 A2 20000725

AB Agents for **treating pain**, methods for producing the agents and methods for **treating pain** by administration to a patient of a therapeutically effective amt. of the agent are disclosed. The agent can include a **clostridial neurotoxin**, or a component or fragment or deriv. thereof, attached to a targeting moiety, wherein the targeting moiety is selected from a group consisting of transmission compds. which can be released from neurons upon the transmission of **pain** signals by the neurons, and compds. substantially similar to the transmission compds. The agent

comprises a **botulinum toxin** component covalently coupled to **substance P**.

L45 ANSWER 20 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:90086 HCAPLUS
DOCUMENT NUMBER: 136:156405
TITLE: Method for structural modifying **Clostridial neurotoxins** for altering biological activity or persistence by leucine-based motifs
INVENTOR(S): Steward, Lance E.; Fernandez-Salas, Ester; Herrington, Todd M.; Aoki, Kei Roger
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008268	A2	20020131	WO 2001-US23122	20010720

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-620840 A 20000721
AB The invention provides a method for structural modifying **botulinum toxin** with leucine-based motifs. Modified **neurotoxin** comprising **neurotoxin** including structural modification, wherein the structural modification alters the biol. persistence, such as the biol. half-life and/or a biol. activity of the modified **neurotoxin** relative to an identical **neurotoxin** without the structural modification. In one embodiment, methods of making the modified **neurotoxin** include using recombinant techniques. In another embodiment, methods of using the modified **neurotoxin** to treat conditions include **treating** various disorders, neuromuscular aliments and **pain**.

L45 ANSWER 21 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:89857 HCAPLUS
DOCUMENT NUMBER: 136:145260
TITLE: **Clostridial toxin** derivatives and methods for **treating pain**
INVENTOR(S): **Donovan, Stephen**
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002007759	A2	20020131	WO 2001-US21984	20010712

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-625098 A 20000725

AB Methods for **treating** a bone tumor, in particular **pain** assocd. with bone tumor, by administration to a patient of a therapeutically effective amt. of an agent are disclosed. The agent may include a **clostridial neurotoxin** component attached to a targeting moiety, wherein the targeting moiety is selected from the group consisting of transmission compds. which can be released from neurons upon the transmission of **pain** signals by the neurons, and compds. substantially similar to the transmission compds.

L45 ANSWER 22 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10234 HCAPLUS
DOCUMENT NUMBER: 136:64160
TITLE: Methods for using **tetanus toxin** for beneficial purposes in animals (mammals)
INVENTOR(S): Sanders, Ira
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000172	A2	20020103	WO 2001-US20523	20010628

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001070219	A5	20020108	AU 2001-70219	20020628

PRIORITY APPLN. INFO.: US 2000-214569P P 20000628
WO 2001-US20523 W 20010628

AB Methods of using **tetanus toxin** to modulate or control neural functions or nonneural cellular activities at selected sites in animals, particularly in mammals, and more particularly in humans, are provided. Pharmaceutical formulations to modulate neural functions or non-neural cellular activities of an animal at selected sites in animals, particularly in mammals, and more particularly in humans are also provided. Uses of **tetanus toxin** in prepn. of medicaments for methods of treating clin. disorders or symptoms of animals, particularly mammals and more particularly humans are also

provided.

L45 ANSWER 23 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:816485 HCAPLUS
DOCUMENT NUMBER: 135:339236
TITLE: Methods for treating bone tumors by local administration of a therapeutically effective amt. of a neurotoxin
INVENTOR(S): **Donovan, Stephen**
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082961	A2	20011108	WO 2001-US13100	20010424
WO 2001082961	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-561106 A 20000428
AB Methods for treating benign tumors by local administration to a patient of a therapeutically effective amt. of a neurotoxin, such as a botulinum toxin, to alleviate **pain** assocd. with the bone tumor and/or to cause necrosis of the tumor.

L45 ANSWER 24 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:762800 HCAPLUS
DOCUMENT NUMBER: 135:322726
TITLE: A pharmaceutical composition containing a nicotine receptor agonist and an analgesic for **treatment** of acute, chronic **pain** and/or neuropathic pain and migraines
INVENTOR(S): Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Sands, Steven Bradley; Watsky, Eric Jacob
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001076576	A2	20011018	WO 2001-IB391	20010316
WO 2001076576	A3	20020620		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2001036943 A1 20011101 US 2000-740307 20001218
PRIORITY APPLN. INFO.: US 2000-195738P P 20000407

AB Oral, parenteral or transdermal compns. are disclosed for the treatment of acute, chronic and/or neuropathic pain. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an analgesic agent and a pharmaceutically acceptable carrier. The analgesic agent is selected from opioid analgesics, NMDA antagonists, **substance P** antagonists, COX 1 and COX 2 inhibitors, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), capsaicin receptor agonists, anesthetic agents, benzodiazepines, skeletal muscle relaxants, migraine therapeutic agents, anticonvulsants, antihypertensives, antiarrhythmics, antihistamines, steroids, caffeine, N-type calcium channel antagonists and **botulinum toxin**. The method of using these compds. and a method of **treating** acute, chronic and/or neuropathic **pain** and migraine in a mammal including a human is also disclosed.

L45 ANSWER 25 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:545729 HCAPLUS
DOCUMENT NUMBER: 135:132453
TITLE: **Clostridial neurotoxin** derivatives attached to targeting moieties, and methods using them for **treating pain**
INVENTOR(S): **Donovan, Stephen**
PATENT ASSIGNEE(S): Allergan Sales, Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053336	A1	20010726	WO 2001-US1529	20010117

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002068699 A1 20020606 US 2001-938112 20010823
PRIORITY APPLN. INFO.: US 2000-489667 A 20000119

AB The invention provides agents for **treating pain**, methods for producing the agents, and methods for **treating pain** by administration to a patient of a therapeutically effective amt. of the agent. The agent can include a **clostridial neurotoxin**, or a component of fragment or deriv. thereof, attached

to a targeting moiety, wherein the targeting moiety is selected from transmission compds. which can be released from neurons upon the transmission of **pain** signals by the neurons, and compds. substantially similar to the transmission compds.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 26 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:706999 HCAPLUS
DOCUMENT NUMBER: 133:261538
TITLE: Use of a lectin or lectin conjugate for modulation of C-fiber activity, and therapeutic use thereof
INVENTOR(S): Foster, Keith Alan; Chaddock, John Andrew; Quinn, Conrad Padraig
PATENT ASSIGNEE(S): Microbiological Research Authority, UK
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000057897	A1	20001005	WO 2000-GB1247	20000331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1165114	A1	20020102	EP 2000-914295	20000331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: GB 1999-7429 A 19990331
WO 2000-GB1247 W 20000331

AB The invention relates to the **treatment** of **pain** and to compds. that modulate C-fiber activity. In particular, the invention relates to the use of a lectin in the manuf. of a medicament for modulation of C-fiber neuron activity, and to lectin conjugates. The lectin conjugates comprise a lectin coupled to a peptide or protein, wherein the peptide or protein is substantially free of **Clostridial neurotoxin** enzyme activity. The invention also concerns methods for manufg. the conjugates. The compds. and compns. described have particular application in the treatment of diseases of which C-fiber activity is a component. Such diseases include **pain**, inflammation, psoriasis and other C-fiber related conditions.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 27 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:249106 HCAPLUS
DOCUMENT NUMBER: 130:276767
TITLE: **Conjugates** of galactose-binding lectins and **clostridial neurotoxins** as analgesics

Kam 09/938,112

INVENTOR(S): Duggan, Michael John; Chaddock, John Andrew
PATENT ASSIGNEE(S): The Speywood Laboratory Limited, UK; Microbiological Research Authority
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9917806	A1	19990415	WO 1998-GB3001	19981007
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2306350	AA	19990415	CA 1998-2306350	19981007
AU 9893574	A1	19990427	AU 1998-93574	19981007
AU 741456	B2	20011129		
ZA 9809138	A	19990527	ZA 1998-9138	19981007
EP 996468	A1	20000503	EP 1998-946571	19981007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001518522	T2	20011016	JP 2000-514674	19981007

PRIORITY APPLN. INFO.: GB 1997-21189 A 19971008
WO 1998-GB3001 W 19981007

AB A class of novel agents that are able to modify nociceptive afferent function is provided. The agents may inhibit the release of **neurotransmitters** from discrete populations of neurons and thereby reduce or preferably prevent the transmission of afferent **pain** signals from peripheral to central **pain** fibers. They comprise a galactose-binding lectin linked to a deriv. of a **clostridial neurotoxin**. The deriv. of the **clostridial neurotoxin** comprises the L-chain, or a fragment thereof, which includes the active proteolytic enzyme domain of the light (L) chain, linked to a mol. or domain with membrane-translocating activity. The agents may be used in or as pharmaceuticals for the **treatment** of **pain**, particularly chronic **pain**.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 28 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:206838 HCAPLUS
DOCUMENT NUMBER: 131:28676
TITLE: Biomedical aspects of **botulinum toxin**
AUTHOR(S): Johnson, Eric A.
CORPORATE SOURCE: Department of Food Microbiology and Toxicology Food Research Institute, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of Toxicology, Toxin Reviews (1999), 18(1), 1-15
CODEN: JTTRD9; ISSN: 0731-3837
PUBLISHER: Marcel Dekker, Inc.

Search completed by David Schreiber 308-4292

Kam 09/938,112

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion with 64 refs. **Clostridium botulinum** produces a potent **neurotoxin**, which causes the neuroparalytic illness in humans and animals known as botulism. Seven immunol. distinct **neurotoxins** are recognized, which are designated by the letters A through G. The different serotypes of **botulinum toxin** vary in the animal species that they affect and the severity and duration of paralysis that they evoke. **Botulinum toxin** type A has become an important pharmaceutical for the **treatment** of segmental movement disorders, spasticity, **pain** syndromes, and various other neuronal disorders. **Botulinum toxin** specifically and tightly binds to cholinergic neurons. Upon endocytosis and internalization into the nerve terminal, the **toxin** acts to block or slow the exocytotic release of **neurotransmitters**, particularly acetylcholine. Selective injection of **botulinum toxin** into neuromuscular regions produces a local weakening of proximal muscles and relief from excessive involuntary muscle contractions. In addn. to directly affecting cholinergic **neurotransmission**, **botulinum toxin** also exerts other poorly understood effects including altering activity of autonomic ganglia. The outstanding properties of **botulinum toxin** as a pharmacol. agent are its specificity for peripheral nerves and its long duration of action. Complications and drawbacks of **botulinum toxin** therapy include immunol. resistance in some patients and diffusion and resulting ptosis of neighboring muscles. These side effects can be avoided by proper purifn. and prepn. of the **toxin** for pharmaceutical use.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 29 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:524661 HCAPLUS
TITLE: A novel expression system in toxigenic **clostridia**.
AUTHOR(S): Johnson, Eric A.; Bradshaw, Marite
CORPORATE SOURCE: Department Food Microbiology and Toxicology, University Wisconsin, Madison, WI, 53706, USA
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), BIOT-001. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Expression of genes of toxigenic **clostridia** in many heterologous hosts is limited by codon bias, posttranslational modifications, and soly. of the products. Our lab. has been studying the expression of domains of **botulinum toxin** type A, which has become an important pharmaceutical for the **treatment** of movement disorders and **pain** syndromes. We have developed systems for genetic anal. and expression of **clostridial** proteins in nontoxigenic mutant strains of C. **botulinum**. A RP4-oriT shuttle **vector** originally developed for C. perfringens was successfully transferred from E. coli to a strain of C. **botulinum** deleted in the **toxin** gene cluster. The light chain of **botulinum neurotoxin** was highly expressed from a **plasmid construct** contg. the recombinant **botulinal** gene for the light chain and an active **clostridial** promoter. This system should be valuable in drug

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development and neuronal targeting.

L45 ANSWER 30 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:134005 HCAPLUS
DOCUMENT NUMBER: 128:281110
TITLE: Target-specific expression of presynaptic mossy fiber plasticity
AUTHOR(S): Maccaferri, Gianmaria; Toth, Katalin; McBain, Chris J.
CORPORATE SOURCE: Laboratory Cellular Molecular Neurophysiology, National Institute Child Health Human Development, Bethesda, MD, 20892-4495, USA
SOURCE: Science (Washington, D. C.) (1998), 279(5355), 1368-1370
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mossy fiber synaptic transmission at hippocampal CA3 pyramidal cells and interneurons was compared in rat brain slices to det. whether mossy terminals are functionally equiv. **Tetanic** stimulation of mossy fibers induced long-term potentiation in pyramidal neurons but was either without effect or it induced depression at synapses onto interneurons. Unlike transmission onto pyramidal neurons, transmission onto interneurons was not potentiated after adenosine 3',5'-monophosphate (cAMP) activation. Furthermore, metabotropic glutamate receptor depression of transmission onto interneurons did not involve cAMP-dependent pathways. Thus, synaptic terminals arising from a common afferent pathway do not function as a single compartment but are specialized, depending on their postsynaptic target.

L45 ANSWER 31 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:640559 HCAPLUS
DOCUMENT NUMBER: 127:298730
TITLE: Peptide neurotoxin analog inhibitors of neurotransmitter secretion by neuronal cells for neural targeting of drugs
INVENTOR(S): Montal, Mauricio
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9734620	A1	19970925	WO 1997-US4393	19970318
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9723348	A1	19971010	AU 1997-23348	19970318
PRIORITY APPLN. INFO.:			US 1996-13599P P	19960318
			WO 1997-US4393 W	19970318

Search completed by David Schreiber 308-4292

Kam 09/938,112

AB The invention consists of peptides which inhibit the secretion of neurotransmitters from synaptic vesicles. The peptides of the invention are believed to mimic the activity of neurotoxins produced by **Clostridium botulinum** and C. **tetani** (including **botulinum** serotypes A, B, C, D, E, F and G). Structurally, the peptides are comprised of amino acid fragments from the substrate binding domains selected from three proteins which bind to form a receptor for docking of synaptic vesicles to the plasma membranes of neuronal cells; i.e., SNAP-25, VAMP-2 and syntaxin. Certain of the inventive peptides exhibit strong inhibitory activity; e.g. 50 % or greater decline in neurotransmitter release is obtained at even nanomolar concns. The peptides are suited for use as substitutes for **Clostridium** neurotoxins in clin. applications and in compds. for targeted delivery of drugs into neural cells.

L45 ANSWER 32 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:743984 HCAPLUS
DOCUMENT NUMBER: 126:1210
TITLE: **Botulin** derivative or other agent able to inhibit neuromodulator secretion by sensory afferent synapses and agent use as **pain** inhibitor
INVENTOR(S): Foster, Keith Alan; Duggan, Michael John; Shone, Clifford Charles
PATENT ASSIGNEE(S): The Speywood Laboratory Limited, UK; Microbiological Research Authority
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9633273	A1	19961024	WO 1996-GB916	19960416
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2218857	AA	19961024	CA 1996-2218857	19960416
AU 9653398	A1	19961107	AU 1996-53398	19960416
AU 705924	B2	19990603		
EP 826051	A1	19980304	EP 1996-910091	19960416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI				
CN 1187217	A	19980708	CN 1996-194505	19960416
BR 9609870	A	19990406	BR 1996-9870	19960416
JP 11504006	T2	19990406	JP 1996-531546	19960416
RU 2165976	C2	20010427	RU 1997-119181	19960416
ZA 9603129	A	19961022	ZA 1996-3129	19960419
NO 9704845	A	19971218	NO 1997-4845	19971020
US 5989545	A	19991123	US 1998-945037	19980112
US 6395513	B1	20020528	US 1999-447356	19991122

PRIORITY APPLN. INFO.:
GB 1995-8204 A 19950421
WO 1996-GB916 W 19960416
US 1998-945037 A2 19980112

AB The invention relates to an agent specific for peripheral sensory

Search completed by David Schreiber 308-4292

afferents. The agent may inhibit the transmission of signals between a primary sensory afferent and a projection neuron by controlling the release of at least one **neurotransmitter** or neuromodulator from the primary sensory afferent. The agent may be used in or as a pharmaceutical for the **treatment** of **pain**, particularly chronic **pain**. An example is **Clostridium botulinum neurotoxin** (BoNT) **conjugates** with nerve growth factor (NGF). The BoNT/NGF conjugate specifically interacts with sensory afferents and the proteinase activity of the BoNT/NGF conjugate cleaves proteins involved in neuromodulator secretion.

L45 ANSWER 33 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:358388 HCAPLUS
DOCUMENT NUMBER: 125:78595
TITLE: Molecular structure and toxic action of **Clostridium botulinum** neurotoxin
AUTHOR(S): Kozaki, Shunji; Kamata, Yoichi
CORPORATE SOURCE: College Agriculture, Osaka Prefecture University, Sakai, 593, Japan
SOURCE: Nippon Saikingaku Zasshi (1996), 51(2), 513-522
CODEN: NSKZAM; ISSN: 0021-4930
PUBLISHER: Nippon Saikin Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 60 refs., on structure and activity of **Clostridium botulinum** neurotoxin, domain structure, toxicity, light chain cellular **target** protein and effect on **neurotransmitter** release, receptor of the neurotoxin, etc.

L45 ANSWER 34 OF 45 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:393016 HCAPLUS
DOCUMENT NUMBER: 122:156835
TITLE: Targeted expression of **tetanus** toxin light chain in Drosophila specifically eliminates synaptic transmission and causes behavioral defects
AUTHOR(S): Sweeney, Sean T.; Broadie, Kendal; Keane, John; Niemann, Heiner; O'Kane, Cahir
CORPORATE SOURCE: Department of Genetics, University of Cambridge, Cambridge, CB2 3EH, UK
SOURCE: Neuron (1995), 14(2), 341-51
CODEN: NERNET; ISSN: 0896-6273
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Tetanus** toxin cleaves the synaptic vesicle protein synaptobrevin, and the ensuing loss of neurotransmitter exocytosis has implicated synaptobrevin in this process. To further the study of synaptic function in a genetically tractable organism and to generate a tool to disable neuronal communication for behavioral studies, the authors have expressed a gene encoding **tetanus** toxin light chain in Drosophila. Toxin expression in embryonic neurons removes detectable synaptobrevin and eliminates evoked, but not spontaneous, synaptic vesicle release. No other developmental or morphol. defects are detected. Correspondingly, only synaptobrevin (n-syb), but not the ubiquitously expressed syb protein, is cleaved by **tetanus** toxin in vitro. Targeted expression of toxin can produce specific behavioral defects; in one case, the olfactory escape response is reduced.

L45 ANSWER 35 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

Search completed by David Schreiber 308-4292

Kam 09/938,112

ACCESSION NUMBER: 2001:269922 BIOSIS
DOCUMENT NUMBER: PREV200100269922
TITLE: Pharmacology and immunology of **botulinum toxin** serotypes.
AUTHOR(S): Aoki, K. R. (1)
CORPORATE SOURCE: (1) Allergan, Inc., Irvine, CA, 92623 USA
SOURCE: Journal of Neurology, (April, 2001) Vol. 248, No. Suppl. 1, pp. I/3-I/10. print.
ISSN: 0340-5354.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Botulinum toxin** preparations can provide patients with a therapeutic modality that may improve both their medical condition and quality of life. The mechanism of action of the various **botulinum toxin** preparations and serotypes is similar: they all block **neurotransmitter** release. The majority of clinical conditions treated are based upon the targeted temporary chemodenervation of the selected organ. The antinociceptive effects of **botulinum toxin** type A (BTX-A), based on preclinical studies and clinical experiences in **treating** movement disorders and other **painful** conditions, will also be reviewed to illustrate how this compound may act as it alleviates the discomfort associated with various conditions. Chronic therapies with preparations with the lowest amount of **neurotoxin** protein provide the best chance for long-term therapy by minimizing the potential of the patient to form neutralizing antibodies. Differences in formulations or serotypes impart unique efficacy and safety profiles and thus does not support a simple dose ratio conversion between products.

L45 ANSWER 36 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:76195 BIOSIS
DOCUMENT NUMBER: PREV200100076195
TITLE: A role for the AHP in metaplasticity.
AUTHOR(S): Tzounopoulos, T. (1); Bissonnette, J. M.
CORPORATE SOURCE: (1) Vollum Institute, OHSU, Portland, OR USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-134.2. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English.
AB Long-term potentiation of synaptic transmission in the hippocampus is the leading experimental model for the synaptic changes that may underlie learning and memory. Interestingly, the ability of a synapse for plastic changes itself displays marked variation and plasticity. This higher form of plasticity, called "metaplasticity" can occur concurrently with synaptic plasticity via identical induction mechanisms. Here, we report that the afterhyperpolarization (AHP, more specifically, its apamin sensitive component) by affecting the degree of activation of NMDA receptors affects the degree and direction of synaptic plasticity in the CA1 area in the hippocampus. The intermediate frequency where no lasting change in transmission occurs, the modification threshold, is shifted to the left in the presence of apamin. This effect appears to be postsynaptic since apamin does not affect basal synaptic transmission, paired-pulse facilitation, and post-**tetanic** potentiation. Additionally,

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blockade of the AHP does not affect metaplasticity in mossy fibers where plasticity is independent of NMDA receptor activation. These findings suggest a new and important synaptic role for potassium channels that underlie the AHP. The AHP is a very popular **target** of modulatory pathways, including **neurotransmitters**. Recognition of the presence of metaplasticity and its mechanisms will provide not only new light on how the brain stores information but also new interpretation on old data, such as the effect of certain neurotransmitters in neuronal excitability.

L45 ANSWER 37 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:290507 BIOSIS
DOCUMENT NUMBER: PREV200000290507
TITLE: **Clostridial toxin** derivatives able to modify peripheral sensory afferent functions.
AUTHOR(S): Foster, Keith Alan (1); Duggan, Michael John; Shone, Clifford Charles
CORPORATE SOURCE: (1) Wiltshire UK
ASSIGNEE: The Speywood Laboratory Ltd., London, UK; Microbiological Research Authority, Wiltshire, UK
PATENT INFORMATION: US 5989545 November 23, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 23, 1999) Vol. 1228, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The invention relates to an agent specific for peripheral sensory afferents. The agent may inhibit the transmission of signals between a primary sensory afferent and a projection neuron by controlling the release of at least one **neurotransmitter** or neuromodulator from the primary sensory afferent. The agent may be used in or as a pharmaceutical for the **treatment** of **pain**, particularly chronic **pain**.

L45 ANSWER 38 OF 45 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:391192 BIOSIS
DOCUMENT NUMBER: BA94:63367
TITLE: DIFFERENCES IN THE TEMPERATURE DEPENDENCIES OF UPTAKE OF **BOTULINUM** AND **TETANUS** TOXINS IN APLYSIA NEURONS.
AUTHOR(S): POULAIN B; DE PAIVA A; DOLLY J O; WELLER U; TAUC L
CORPORATE SOURCE: LABORATOIRE NEUROBIOLOGIE CELLULAIRE MOLECULAIRE, CNRS, 91198 GIF-SUR-YVETTE, FR.
SOURCE: NEUROSCI LETT, (1992) 139 (2), 289-292.
CODEN: NELED5. ISSN: 0304-3940.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The respective neuroselective actions of **botulinum** type (BoNT) and **tetanus** (TeTx) neurotoxins on cholinergic and non-cholinergic synapses of Aplysia are mainly due to differences in their extracellular neuronal targetting. Further information was gained on this neuroselectivity by examining the temperature dependencies of binding, internalization and intracellular action of both toxins. After reduction of temperature from 22.degree.C to 10.degree.C, the binding of neither BoNT nor TeTx was significantly altered whereas the neuronal uptake of BoNT, but not of TeTx, was prevented. Although TeTx internalization could be detected at the low temperature, its intracellular activity was greatly attenuated compared to that of BoNT. It is inferred that the uptake

mechanisms are different for these two related but distinct toxins.

L45 ANSWER 39 OF 45 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001118339 EMBASE
TITLE: **Botulinum toxin** A in the **treatment** of headache syndromes and pericranial **pain** syndromes.
AUTHOR: Gobel H.; Heinze A.; Heinze-Kuhn K.; Austermann K.
CORPORATE SOURCE: H. Gobel, Kiel Pain Clinic, Heikendorfer Weg 9-27, D-24149 Kiel, Germany. kiel@schmerzklinik.de
SOURCE: Pain, (2001) 91/3 (195-199).
Refs: 48
ISSN: 0304-3959 CODEN: PAINDB
PUBLISHER IDENT.: S 0304-3959(01)00292-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English

L45 ANSWER 40 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:743334 SCISEARCH
THE GENUINE ARTICLE: 472ZB
TITLE: **Botulinum toxin therapy** for **pain** and inflammatory disorders: mechanisms and **therapeutic** effects
AUTHOR: Borodic G E (Reprint); Acquadro M; Johnson E A
CORPORATE SOURCE: Harvard Univ, Sch Med, Massachusetts Eye & Ear Infirm, Dept Ophthalmol, Boston, MA 02115 USA (Reprint); Harvard Univ, Massachusetts Gen Hosp, Sch Med, Dept Anesthesia, Boston, MA 02114 USA; Univ Wisconsin, Dept Food Microbiol & Toxicol, Inst Food Res, Madison, WI USA
COUNTRY OF AUTHOR: USA
SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (AUG 2001) Vol. 10, No. 8, pp. 1531-1544.
Publisher: ASHLEY PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND.
ISSN: 1354-3784.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 92
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Botulinum toxin** (BTX) injections are a well-recognised therapeutic modality for the treatment of regional involuntary muscle disorders and recently BTX has been used for **treatment** of **pain** and inflammatory disorders. The primary purpose of this review is to discuss the mechanism of action of therapeutic BTX in light of both the traditional understanding of BTX pharmacological effects as well as new observations. The review will deal with clinical observations and relevant animal experimentation. The data and hypotheses presented are not only relevant to **botulinum toxin** technology but will certainly prove important in the basic mechanisms of some of the diseases where **botulinum toxin** has been successfully applied. BTX used clinically comprises **botulinum neurotoxin** (BoNT) complexed with non-toxic proteins. The non-toxic components of the BTX complexes stabilise the labile BoNT during purification and formulation as a therapeutic. The complex proteins may also have unrecognised clinical significance such as slowing diffusion in tissues or imparting stability. The mechanisms of BTX

formulations acting on SNARE proteins are briefly reviewed providing a basis for BTX clinical applications. The potential for design of improved **botulinum toxins** and formulations is addressed.

L45 ANSWER 41 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:782602 SCISEARCH
THE GENUINE ARTICLE: 243NU
TITLE: Functional circuitry for the induction of prolonged excitation in the rat spinal dorsal horn
AUTHOR: Murase K (Reprint); Saka T; Asai T; Ikeda H
CORPORATE SOURCE: FUKUI UNIV, DEPT HUMAN & ARTIFICIAL INTELLIGENT SYST, 3-9-1 BUNKYO, FUKUI 9108507, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (SEP 1999) Vol. 11, No. 9, pp. 3355-3358.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 ONE, OXON, ENGLAND.
ISSN: 0953-816X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The neuronal circuitry through which prolonged excitation is generated in the spinal dorsal horn was investigated using optical imaging of neuronal excitation in transverse slices of rat spinal cords. It is known that **tetanic** stimulation (20 Hz for 1 s) of the dorsal root that activates both A and C primary afferent fibres elicits slow intrinsic optical signals (IOS) in the dorsal horn, seen most intensely in the substantia gelatinosa (SG), lamina II, and that IOS **expresses** in part the slow synaptic response recorded intracellularly in dorsal horn neurons. We here report that the slow IOS within the SG were completely abolished after an incision was made at the border between the SG and the deeper laminae, but not after an incision within the deeper dorsal horn of the laminae III-V. The result demonstrates directly that, in order to generate prolonged excitation in the SG, the neuronal elements in the deeper dorsal horn must be intact. Thus, the afferent information might be received first by the deeper elements and then transmitted to the SG region, and/or collaboration between the SG and deeper elements is necessary to maintain prolonged excitation in the SG.

L45 ANSWER 42 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:90542 SCISEARCH
THE GENUINE ARTICLE: 158WH
TITLE: Unilateral joint inflammation induces bilateral and time-dependent changes in neuropeptide FF binding in the superficial dorsal horn of the rat spinal cord: implication of supraspinal descending systems
AUTHOR: Lombard M C; WeilFugazza J; Ries C; Allard M (Reprint)
CORPORATE SOURCE: UNIV BORDEAUX 2, INSERM U378, INST FRANCOIS MAGENDIE, 1 RUE CAMILLE ST SAENS, F-33076 BORDEAUX, FRANCE (Reprint); UNIV BORDEAUX 2, INSERM U378, INST FRANCOIS MAGENDIE, F-33076 BORDEAUX, FRANCE; INSERM U161, F-75014 PARIS, FRANCE; EPHE, LAB PHYSIOPHARMACOL DOULEUR, F-75014 PARIS, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: BRAIN RESEARCH, (23 JAN 1999) Vol. 816, No. 2, pp. 598-608
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE

Search completed by David Schreiber 308-4292

AMSTERDAM, NETHERLANDS.
ISSN: 0006-8993.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Using quantitative autoradiography, the effects of acute and chronic inflammation on specific I-125-1DMethyl-FLFQPQRFamide binding were investigated in the rat spinal cord dorsal horn superficial layers, at 6 and 24 h and 2, 4, 6 and 12 weeks after induction of monoarthritis produced by injection of killed Mycobacterium **butyricum** suspended in Freund adjuvant in one tibio-tarsal joint. Six hours after monoarthritis induction, no modification in specific I-125-1DMethyl-FLFQPQRFamide binding was observed, whereas a significant bilateral increase occurred after 24 h and 2 weeks in L4/L5 dorsal hems, with a return to control values at 4, 6 and 12 weeks. Specific I-125-1DMethyl-FLFQPQRFamide binding was also investigated 24 h after monoarthritis induction in rats submitted 4 days before the induction to spinal cord lesions at the thoracic level (T9-T10). Hemisection of the spinal cord contralateral to the affected ankle prevented the transient bilateral increase in specific I-125-1DMethyl-FLFQPQRFamide binding, whereas total spinal cord section induced a significant bilateral decrease. All of these modifications were restricted to the spinal segments receiving afferent input from the arthritic ankle (L4/L5); no modifications were found at the levels L1 or CG-Cs. These data suggest that FLFQPQRFamide is involved in spinal nociceptive processing during sustained peripheral nociceptor activation. The effects of spinal cord lesions in monoarthritic rats indicate that the modifications seen in the FLFQPQRFamide system activity, during sustained peripheral inflammation, depend on afferent fiber activation as well as on supraspinal controls.

L45 ANSWER 43 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:593617 SCISEARCH
THE GENUINE ARTICLE: 105KD
TITLE: Pharmacological evaluation of 1-(carboxymethyl)-3,5-diphenyl-2-methylbenzene, a novel arylacetic acid with potential anti-inflammatory properties
AUTHOR: Cutler S J; Blanton C D; Akin D T; Steinberg F B; Moore A B; Lott J A; Price T C; May S W; Pollock S H (Reprint)
CORPORATE SOURCE: MERCER UNIV, DEPT PHARMACEUT SCI, 3001 MERCER UNIV DR, ATLANTA, GA 30341 (Reprint); MERCER UNIV, DEPT PHARMACEUT SCI, ATLANTA, GA 30341; UNIV GEORGIA, COLL PHARM, DEPT MED CHEM, ATHENS, GA 30602; GEORGIA INST TECHNOL, SCH CHEM & BIOCHEM, ATLANTA, GA 30332
COUNTRY OF AUTHOR: USA
SOURCE: INFLAMMATION RESEARCH, (JUL 1998) Vol. 47, No. 7, pp. 316-324.
Publisher: BIRKHAUSER VERLAG AG, PO BOX 133 KLOSTERBERG 23, CH-4010 BASEL, SWITZERLAND.
ISSN: 1023-3830.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective and Design: 1-(Carboxymethyl)-3,5-diphenyl-2-methylbenzene (CDB), a novel arylacetic acid, was evaluated in vivo for its ability to

inhibit acute and chronic inflammation as well as acute **pain**.

Materials and Methods: The effects of CDB were evaluated using the following assays: 1) acute inflammation induced by the injection of carrageenan, bradykinin and serotonin into the subplantar region of the hind paw of rats; 2) chronic inflammation produced by the injection of Mycobacterium **butyricum** into the base of the tail of rats; 3) acute **pain** induced by the i.p. injection of phenyl-p-quinone into mice resulting in the production of writhes; 3) cyclooxygenase (COX) activity, including COX-1 and COX-2, evaluated using whole blood; and 5) activity of peptidylglycine alpha-monooxygenase (PAM) isolated from Xenopus laevis skin.

Results: CDB (10 to 100 mg/kg s.c.) produced a dose-dependent inhibition of carrageenan edema (ED50 of 41 mg/kg at 3 h) which continued for up to 12 h. Using a therapeutic dosing regimen, this compound inhibited hind paw inflammation (>70%) and arthogram scores in rats with adjuvant-induced arthritis. This compound also possessed significant analgesic activity in mice (70% inhibition with 50 mg/kg). CDB, however, lacked inhibitory activity on bradykinin and serotonin-induced edema. In addition, CDB significantly inhibited COX-1 activity (IC50 congruent to 17 mu M) while having only a weak inhibitory activity on both COX-2 and PAM activity.

Conclusions: CDB is an effective anti-inflammatory/analgesic agent whose mechanism of action appears to be associated with inhibition of COX-1 activity.

L45 ANSWER 44 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:453101 SCISEARCH
THE GENUINE ARTICLE: UQ243
TITLE: IMMUNOPHILIN REGULATION OF NEUROTRANSMITTER RELEASE
AUTHOR: STEINER J P; DAWSON T M; FOTUHI M; SNYDER S H (Reprint)
CORPORATE SOURCE: JOHNS HOPKINS UNIV, SCH MED, DEPT NEUROSCI, 725 N WOLFE ST, BALTIMORE, MD, 21205 (Reprint); JOHNS HOPKINS UNIV, SCH MED, DEPT NEUROSCI, BALTIMORE, MD, 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT PHARMACOL, BALTIMORE, MD, 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT MOLEC SCI, BALTIMORE, MD, 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT PSYCHIAT, BALTIMORE, MD, 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT BEHAV SCI, BALTIMORE, MD, 21205; GUILFORD PHARMACEUT INC, DEPT NEUROBIOL, BALTIMORE, MD, 00000; HARVARD UNIV, SCH MED, DEPT NEUROSCI, BOSTON, MA, 00000
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR MEDICINE, (MAY 1996) Vol. 2, No. 3, pp. 325-333. ISSN: 1076-1551.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 24

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The immunophilins are proteins that mediate actions of immunosuppressant drugs such as FK506 and cyclosporin A by binding to calcineurin, inhibiting its phosphatase activity, and increasing the phosphorylation level of transcription factors required for interleukin 2 formation. Though concentrations in the brain greatly exceed levels in immune tissues, no function has been previously established for nervous system immunophilins. Nitric oxide (NO) has been implicated in neurotransmitter release. FK506 appears to inhibit NO production by maintaining NO synthase in a highly phosphorylated and thereby inactivated state. Accordingly, we examined effects of FK506 and cyclosporin A on neurotransmitter release in PC12 cells treated with nerve growth factor

(NGF) and in rat brain stratal synaptosomes.

Materials and Methods: We monitored effects of immunophilin ligands on [H-3]-neurotransmitter release from PC12 cells differentiated with NGF. Rat brain striatal synaptosomes were loaded with radiolabeled transmitters and treated with FK506 or cyclosporin A prior to initiating neurotransmitter release with N-methyl-D-aspartate (NMDA) or potassium depolarization. Striatal synaptosomes were also loaded with P-32-orthophosphate and treated with FK506. P-32-labeled synaptic vesicle proteins were isolated from these synaptosomes in an attempt to relate specific FK506-dependent phosphorylation of vesicle proteins with the effects of FK506 on **neurotransmitter** release. Identification of proteins **targetted** by FK506 was made by immunoblot analysis and immunoprecipitation.

Results: Low nanomolar concentrations of the immunosuppressant drugs FK506 and cyclosporin A (CsA) inhibit transmitter release from PC-12 cells and from NMDA-stimulated brain synaptosomes. By contrast, the immunosuppressants augment depolarization-induced transmitter release from synaptosomes. synapsin I, a synaptic vesicle phosphoprotein, displays enhanced phosphorylation in the presence of FK506.

Conclusions: Inhibition of transmitter release in PC-12 cells and NMDA-treated synaptosomes by immunosuppressants may reflect augmented phosphorylation of NO synthase, reducing its catalytic activity. This fits with the requirement of NO for transmitter release in PC12 cells and NMDA-treated synaptosomes. Stimulation by immunosuppressants of transmitter release in potassium depolarized synaptosomes may result from augmented phosphorylation of synapsin I, whose phosphorylation is known to facilitate transmitter release. Thus, immunophilins may modulate release of numerous neurotransmitters both by influencing NO formation and the phosphorylation state of synaptic vesicle-associated proteins.

L45 ANSWER 45 OF 45 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:443241 SCISEARCH
THE GENUINE ARTICLE: UP705
TITLE: EFFECT OF ACUTE STIMULATION ON FOS **EXPRESSION** IN SPINAL NEURONS IN THE PRESENCE OF PERSISTING C-FIBER ACTIVITY
AUTHOR: LEAH J D (Reprint); PORTER J; DEPOMMERY J; MENETREY D; WEILFUGUZZA J
CORPORATE SOURCE: GRIFFITH UNIV, SCH SCI, NATHAN, QLD 4111, AUSTRALIA (Reprint); INSERM U161, F-75014 PARIS, FRANCE
COUNTRY OF AUTHOR: AUSTRALIA; FRANCE
SOURCE: BRAIN RESEARCH, (06 MAY 1996) Vol. 719, No. 1-2, pp. 104-111.
ISSN: 0006-8993.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 61

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Expression** of the inducible transcription factor c-Fos has been examined in the lumbar spinal cord following noxious chemical stimulation (injection of 2% formalin) of the ankles or the ventral skin of the hindpaws of either normal rats, or monoarthritic rats during the chronic phase of the disease. In normal animals the basal **expression** of c-Fos was low. One day after induction of monoarthritis by an intra-articular injection of killed Mycobacterium **butyricum** (in complete Freund's adjuvant) there were numerous c-Fos labelled cells in the ipsilateral dorsal horn, and bilaterally in lamina VIII and in other areas of the ventral horn. Four weeks after

induction of the arthritis, although marked inflammation of the ankle was still present, all the **expression** of c-Fos had returned to the basal levels. One hour after formalin stimulation of the ankle or hindpaw skin of normal rats **expression** of c-Fos was observed throughout the ipsilateral, but not contralateral dorsal hem. Formalin stimulation of the inflamed ankle in four-week arthritic rats induced a 3-to-6 fold increase in c-Fos **expression** in the ipsilateral dorsal horn compared to formalin stimulation of the ankle in normal rats. In addition, c-Fos **expression** was induced in the contralateral deep, but not superficial laminae, at a density similar to that produced ipsilaterally by formalin stimulation of the ankle of normal rats. Formalin stimulation of the contralateral ankle in monoarthritic rats (i.e. the non-inflamed ankle) induced an ipsilateral **expression** of c-Fos which was similar to that observed after stimulation of the arthritic ankle. This stimulation of the normal ankle also resulted in an **expression** of c-Fos in the contralateral deep, but not superficial laminae, that was similar to that induced ipsilaterally by stimulation of the arthritic ankle. Finally, formalin stimulation of the hindpaw skin (which was not inflamed) of the arthritic limb induced the same number of c-Fos labelled cells in the superficial laminae as did formalin stimulation of the skin of normal rats; but in the deep laminae there was a 1.6-fold increase in the number of labelled cells. These different observations show that the down-regulation of c-Fos **expression** observed in chronic monoarthritis is in fact associated with a sensitization and an extension of the field of its **expression** in response to an acute nociceptive stimulation.